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Improvement in neuroleptic-induced akathisia with intravenous iron treatment in a patient with iron deficiency

Iron deficiency may play a role in the pathogenesis of drug-induced akathisia, but the evidence is conflicting.[1–3] There have been no reports of the effect of iron treatment in this condition. We report the case of a patient with iron deficiency whose akathisia had not responded to standard interventions but did respond dramatically to intravenous iron treatment.

A 68-year-old man with schizophrenia had been well controlled for 10 years on thioridazine 150 mg/day. His treatment was changed to respiridone 1 mg twice daily. Within 2 weeks, he had developed a severe sensation of inner restlessness and anxiety associated with increased leg movements and body rocking. No depressive or psychotic symptoms were noticed, although the patient was greatly distressed. Acute drug-induced akathisia was diagnosed.

No improvement in akathisia symptoms was noticed when the dose of respiridone was reduced or when respiridone was discontinued and thioridazine restarted. Therapeutic trials of alprazolam, benztropine and propranolol failed to alleviate his symptoms and led to side effects.

When seen in our clinic, the patient had had symptoms for >6 months. He reported a ''terrible feeling'' of restlessness and anxiety ''gnawing inside me'' each day. Symptoms were present throughout the day, with no worsening at night, and no limb paraesthesias were noticed. There was no personal or family history suggestive of restless legs syndrome (RLS). Neurological examination was normal apart from reduced facial expressiveness. The Barnes Akathisia Rating Scale (BARS), a well-validated scale of akathisia severity comprising objective and subjective components, was 11/14, which is consistent with severe akathisia.[2]

Electrolytes, serum urea, creatinine and glucose, thyroid function tests, erythrocyte sedimentation rate, C reactive protein, vitamin B_{12}, and folate levels were normal. Haemoglobin was 13.1 g% (abnormal in our laboratory <13 g%), transferrin saturation 12% (abnormal <15%), serum ferritin 36 μg/l (abnormal <12 μg/l), total iron-binding capacity 490 μg/l (abnormal >400 μg/l) and serum iron 520 μg/l (abnormal <600 μg/l). A diagnosis of iron deficiency was made on the basis of the abnormal transferrin saturation combined with a serum ferritin <50 μg/l.[4] Gastrointestinal examination was normal and serial tests for faecal occult blood were negative. He had a distant history of peptic ulcer disease. Dietary history showed inadequate intake of iron-containing foods. His dentition was poor. The patient refused endoscopic investigation of the intestinal tract. Screening tests for coeliac disease were negative.

Oral iron supplements caused unacceptable nausea and epigastric discomfort. The patient was given 400 mg intravenous ferrous sucrose in divided doses (100 mg in 100 ml normal saline on days 1 and 3, and 200 mg on day 5). On day 7, the patient reported that he felt normal for the first time in months. The BARS score was now 3/14 (corresponding to mild or questionable akathisia); haemoglobin was 13.8 g%, ferritin 52 μg/l and transferrin saturation 17%. Dietary advice was given to increase the intake of iron-containing food. Subsequently, he was able to tolerate 300 mg ferrous gluconate (containing 35 mg of elemental iron) every second day. Clinical (BARS score 3/14) and haematological (haemoglobin 13.7 g% and ferritin 68 μg/l) improvement were maintained on review at 5 months.

Both akathisia and RLS are characterised by motor restlessness and sleep disturbances, and RLS can be precipitated by dopamine-blocking drugs. There is convincing evidence that iron status is an important factor in the pathogenesis of RLS, and correction of iron deficiency improves symptoms in RLS.[5] The balance of evidence from previous studies does not suggest that iron deficiency plays a similarly critical role in the development of drug-induced akathisia in most patients. However, many studies either focused on serum iron,[1 2] which is not a good guide to iron status, or used an inappropriately low cut-off for normal serum ferritin.[4] Nevertheless, studies that examined ferritin levels reported that patients with akathisia had lower levels than controls without akathisia.[3]

Studies comparing blood tests with bone marrow examination have shown that serum ferritin at a cut-off of 50 μg/l is the best screening test for iron deficiency in patients with and without anaemia.[4] Furthermore, serum ferritin <50 μg/l has also proved useful for predicting responsiveness to iron supplementation in people with RLS.[5]

The patient in this report had several haematological indices suggestive of iron deficiency and several risk factors for iron deficiency. His serum ferritin of 36 μg/l is also consistent with mild iron deficiency. His haemoglobin level of 13.1 g% was at the low end of normality for a man. As a general rule, 8 mg of storage iron corresponds to 1 μg/l ferritin. Thus, in an iron replete person, 400 mg of intravenous iron would lead to a rise in serum ferritin of about 50 μg/l; the relatively small rise in ferritin levels in our patient suggests that the iron supplement was indeed used to correct a tissue deficiency in iron.

It is unlikely that this patient had an atypical RLS. No night-time worsening of symptoms (a necessary diagnostic feature in RLS) was noticed. The feeling of inner restlessness and body rocking are characteristic of acute drug-induced akathisia. It is not uncommon for akathisia, once provoked, to fail to resolve when the precipitating drug change is reversed.

The close temporal relationship between administration of intravenous iron and resolution of hitherto resistant symptoms in our patient suggests that iron deficiency can contribute to the development or persistence of akathisia in some patients. Iron repletion may be valuable in such cases, although this requires further evaluation. There are, of course, other potential benefits to treating and identifying the cause of iron deficiency. We suggest that haemoglobin, serum ferritin and transferrin saturation should be checked in patients with akathisia, and that patients with iron deficiency should be treated until haemoglobin is normal and serum ferritin is more than 50 μg/l. Although the use of intravenous iron formulations may facilitate examination of the potential effects of iron repletion on akathisia in future studies, biochemical improvement is usually seen within 2–4 weeks of starting oral iron supplements in patients with deficiency and this should remain the initial treatment.

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Guillain–Barré syndrome with antibodies to GD1a/GD1b complex

Recently, ganglioside complexes (GSCs) such as GD1a/GD1b, GD1a/GM1, GD1b/GT1b, GM1/GT1b, GQ1b/GM1 and GQ1b/GD1a have been

shown as target antigens for serum antibodies in patients with Guillain–Barré syndrome (GBS)[1] and Miller Fisher syndrome (MFS).[2] Gangliosides may interact with each other to form a novel epitope, which serves as a target antigen for serum antibodies.[1] In paticular, anti-GD1a/GD1b IgG is reported to be associated with severe GBS and requirement of mechanical ventilation.[1] However, there has been no previous case report describing GBS with anti-GSC antibodies in detail. In this report, we present a patient with GBS having anti-GD1a/GD1b antibody and investigated the clinical feature.

Case report

A 42-year-old man noticed weakness of the bilateral upper extremities 2 weeks after an episode of acute respiratory tract symptoms and diarrhoea. His symptoms further developed to dysarthria, dysphagia and tetraparesis, and he was admitted to the Department of Neurology, Ishikawa Prefecture Central Hospital, Kanazawa, Japan, 4 days after the onset of weakness. Neurological examination disclosed bilateral facial weakness, poor elevation of the soft palate, hoarseness, dysarthria, dysphagia, weakness of the tongue, flaccid tetraparesis (grade 4, Medical Research Council scale) and areflexia of deep tendon reflexes. He needed a wheelchair for transfer, and stomach tube for gastrogavage. Laboratory findings including cerebrospinal fluid (CSF) examination were normal, except for hypercapnia (P_{CO_2} 47.8 mm Hg) on blood gas analysis. Nerve conduction studies demonstrated a marked reduction of compound muscle action potentials (CMAP) with normal conduction velocity (CMAP was 2.87 mV and motor conduction velocity was 50.6 m/s in the right median nerve), but sensory nerves were normal. The MRI studies of the brain and spinal cord were normal. A diagnosis of GBS was made, and he was given intravenous immunoglobulin (IVIg; 400 mg/kg/day) and intravenous methylprednisolone (500 mg/day) for 5 days, according to the protocol used in the previously reported randomised trial.[3] He underwent rehabilitation, and his symptoms gradually improved 1 week after admission. He could stand by himself 2 weeks after admission, and eat by himself without a stomach tube 1 month after admission. Nerve conduction studies still showed simple reduction of CMAPs 1 month after admission (CMAP was 1.21 mV and motor conduction velocity was 53.0 m/s in the right median nerve). At 2 months after admission, he could ambulate independently. He returned to work (English teacher at a high school) 3 months after admission.

The antibodies to gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, GA1, Gal-C, and GalNac-GD1a) and GD1a/GD1b complex in the serum obtained on the first day of admission were examined by enzyme-linked immunosorbent assay, as previously described.[1 4] He was positive only to the antibody to GD1a/GD1b complex (anti-GD1a/GD1b antibody).

Comment

Our patient showed acute progressive axonal motor polyneuropathy involving the cranial nerves 2 weeks after flu-like symptoms. This condition fulfilled the established criteria of GBS, and the results of nerve conduction studies were classified as having acute motor axonal neuropathy (AMAN).[5] Anti-GD1a/GD1b antibody was detected in the acute-phase serum; however, there were no antibodies to single gangliosides, including GD1a and GD1b.

In a recent report,[1] 8 of 100 patients with GBS had anti-GD1a/GD1b antibodies, and three of these eight did not demonstrate any anti-ganglioside antibodies. These eight patients with anti-GD1a/GD1b antibody tended to have cranial nerve deficits and severe disabilities, and four of these patients required artificial ventilation.[1] Of the three anti-GD1a/GD1b antibody-positive patients with available electrophysiological data, two showed an axonal neuropathy pattern, and the remaining one showed an equivocal pattern.[1] Of the 12 patients with MFS, 7 had serum antibodies to some GSCs, and anti-GSC antibodies might influence the clinical features, as sensory signs were infrequent in patients with anti-GQ1b/GM1 antibody.[2] These findings may support the theory that anti-GSC antibodies correlate with a certain phenotype of GBS or MFS.

The clinical features of our patient were similar to those patients with anti-GD1a/GD1b antibodies,[1] such as AMAN-type GBS with cranial nerve deficits and severe disability (the Hughes Functional Grading Scale at the peak of his disability was on grade 4). Although our patient did not require artificial ventilation, his hypercapnia suggested respiratory weakness. The patient received intravenous methylpredonisolone in addition to IVIg. This combination therapy might prevent his case from being aggravated to grade 5. However, a future large-scale study will be needed to clarify this point.

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Putaminal petechial haemorrhage as the cause of non-ketotic hyperglycaemic chorea: a neuropathological case correlated with MRI findings

Acute generalised chorea can be attributed to multiple causes, including non-ketotic hyperglycaemia. This cause has been associated with characteristic image signs of striatal hyperdensity on CT scan and hyperintensity on T1 weighted (T1W) MRI.

We report a patient presenting with this syndrome in which a postmortem study was conducted. The findings are discussed together with the neuropathological data available in the literature, contributing towards an explanation of the nature of the imaging signs that has remained elusive.

Case report

A 73-year-old woman was admitted to our neurological department for acute generalised chorea of 8 days' duration. There was no relevant personal background or family history.

On admission, the patient presented with orofacial dyskinesias and choreic movements in the neck, trunk, upper and lower limbs. The aetiological diagnostic work-up for acute chorea revealed severe hyperglycaemia on admission (>27.8 mmol/l), bicytopenia with anaemia (erythrocyte count $2.8\times10^6/mm^3$, haemoglobin 8.1 g/dl) and thrombocytopenia (104 000/μl), and an isolated antiphospholipid antibody positive titre. The remaining investigation for acute chorea was normal. The imaging studies revealed a spontaneous bilateral hyperdensity in the putamen and caudate nuclei on the admission brain CT scan. The brain MRI (1.5T; Signa Horizon, General Electrics Medical Systems, Milwaukee, Wisconsin, USA), conducted 2 weeks after admission, showed a bilateral putaminal hyperintensity in T1W images exclusively (fig 1).

Chorea persisted beyond glycaemia normalisation. The patient eventually died 32 days after admission as a result of unresolved sepsis, having begun with fever 4 days after admission. A postmortem examination was conducted.

In the neuropathological study, paraffin embedded representative sections of the left hemisphere, brainstem and cerebellum were stained with haematoxylin–eosin, Bodian–Luxol, Perls and Van Gieson stains. The basal ganglia region was studied using anterior and posterior coronal sections. Microscopic examination revealed generalised wall fibrosis of the small perforating arteries associated with dilatation of the perivascular spaces of the deep white matter. Multiple lacunes in the basal ganglia and thalamus were found in association with macrophage proliferation. Astrocytic gliosis and extravascular hemosiderin deposits together with ferruginateous deposits on perforating vessels were observed in the posterior zone of the putamen. No vascular amyloid or calcium deposits were observed.

Discussion

In our case, the triad of acute chorea, non-ketotic hyperglycaemia and a hyperdense and hyperintense putamen on CT and T1W MRI was documented. The bicytopenia and an antiphospholipid antibody positive titre could